Functional Ovarian Tumors*

A Ten Year Study at Freedmen's Hospital

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DURING the ten year period from July 1952 through June 1962, 462 ovarian tumors were found at Freedmen's Hospital. Of these 462 tumors, 34 were solid and of the solid tumors, 14 belonged to the functional group. Functioning ovarian tumors are tumors which exhibit low grade malignant tendencies, have the characteristics of functional endocrine activity and are capable of producing interesting biological phenomena of one sort or another.

It is generally accepted that the microscopic appearance, although sometimes uncertain, should be the criterion for classification rather than the endocrine effects produced by such tumors. Functional ovarian tumors are usually classified as being either feminizing or masculinizing. The granulosa cell and the theca cell tumors are considered feminizing and the luteoma is thought to represent the complete or partial luteinization of the thecoma or granulosa cell tumor. In our series there were seven granulosa cell tumors, three thecomas and one luteoma. However, one of the thecomas in this series was accompanied by masculinizing symptoms.

Some 325 thecomas have been reported in the literature. However, less than a dozen have been implicated as being associated with clinical virilization. Virilization in association with a granulosa cell tumor is even a rarer event and an incomplete review of the literature in 1959 disclosed only four of these tumors.[1] Other tumors belonging to the masculinizing group are arrhenoblastomas, adrenal rest tumors and hilar cell tumors. The gynandroblastoma, though usually virilizing, has components of both the granulosa cell tumor and arrhenoblastoma. Of the masculinizing tumors, our series contains one arrhenoblastoma, one hilus cell tumor and one gynandroblastoma.

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FEMINIZING TUMORS

The granulosa cell tumor is the most common of the functioning tumors of the ovary. This tumor may occur at any time from early childhood to the geriatric age group, with tumors being reported at 14 months and 85 years.[2-3] It is estimated that these tumors represent approximately 20 per cent of the solid ovarian tumors. They are usually unilateral and are rarely larger than an orange and frequently smaller. However, a tumor weighing 32 pounds has been reported.[4] Histologically, these tumors present extremely variable patterns. Characteristically, the cells are basophilic in nature with disproportionately large dark staining nuclei. Call-Exner bodies, which are small areas of cystic liquefaction, are often present. These bodies are characteristic of granulosa cells.

The thecoma is much rarer than the granulosa cell tumor, but grossly they are usually indistinguishable. Since almost 70 per cent of the thecomas are found in the postmenopausal patient, the possibility of their occurrence should be suspected more frequently in this age group. This tumor rarely occurs in childhood.[5] Microscopically, the thecoma is characterized by bundles of spindle cells which tend to resemble connective tissue cells. Unless fat stains are used it is almost impossible to distinguish between the thecoma and fibroma of the ovary. Fat stains with the finding of doubly refractile intracellular fat are, to a great extent, the criterion for distinguishing thecomas from fibromas.

Clinically, the effects of the granulosa-theca cell tumors are most striking prior to the menarche and after the menopause. In the young girl, precocious puberty may manifest itself with breast enlargement and early development of other secondary sex characteristics. There may be rapid body growth but early closure of the bony epiphysis. Early en-

largement and function of the uterus with irregular and excessive uterine bleeding are present.

In the postmenopausal woman there is a return of uterine bleeding; the uterus enlarges; there is an increase in the size of the breasts, and thickening of the vaginal mucosa.

If the tumor develops during menstrual life there are no added feminizing manifestations, although there may be an increase in the amount of genital bleeding or even amenorrhea may be present.

The above are classical signs and symptoms of feminizing ovarian tumors. However, it should be pointed out 40 per cent of the granulosa cell and theca cell tumors have no hormonal activity.[6]

The malignant potential of a granulosa cell tumor is about six times that of a thecoma. The reported malignancy rate of the former is 20-30 per cent, while that of the thecoma is from 3-5 per cent. However, the association with endometrial carcinoma is much more frequent with thecomas.

Of the nine cases in our series which belong to the granulosa-theca cell group (excluding the thecoma which was associated with virulization), the average age was 44 years with a range of 33-59 years. Thus, one would not expect to find striking femininizing changes in this group. The signs and symptoms in our cases were:

1. Menorrhagia.
2. Postmenopausal bleeding.
3. Lower abdominal pain.
4. Ascites.
5. A rapidly enlarging abdominal mass.

Four cases, all granulosa cell tumors, showed sign of malignancy at surgery. A typical case in this group is that of:

C. S., No. 147-443: Admitted: June 18, 1958.

This is a 43-year-old nulligravida whose last normal menstrual period was in April 1958. On admission she gave a history of having had prolonged menses with a heavy flow for two months' duration. Associated with this was a rapidly growing abdominal mass. Menarche—age 12, Cycle—28 days, Duration 3-4 days, with a moderate flow.

Past History: Right salpingo-oophorectomy for a ruptured TOA (tubo-ovarian abscess) in 1956. Physical examination was essentially negative except for the abdomino-pelvic findings which showed a mass which was enlarged to approximately six months' gestation.

At surgery the mass was found to measure 20x15x14.5 cm., and was reported microscopically as granulosa cell carcinoma with infiltration to the left Fallopian tube.

MASCULINIZING TUMORS

The most striking symptoms produced by ovarian tumors are those produced by the masculinizing group. These tumors almost always appear during the reproductive life of a woman. They are extremely rare in the adolescent and postmenopausal periods. The youngest case of an arrhenoblastoma reported is that of a 14-year-old girl and the oldest case was 66 years.[6] Signs and symptoms of masculinizing tumors usually take place in two definite phases, an early phase of defeminization and a subsequent phase of masculinization. Typically, a menstruating female will first notice oligomenorrhea or amenorrhea. There is regression of the breasts and external genitalia, atrophy of the uterus and adnexa, and loss of the female body contour. This is followed by hirsutism, acne, clitoral enlargement, increased libido, sterility, enlargement of the larynx, deepening of the voice and temporal alopecia.

On the other hand, these tumors may produce little or no androgenic activity. In fact, hypermenorrhea (as in our case) and endometrial hyperplasia have been associated with arrhenoblastomas and cases have been reported in which pregnancy and arrhenoblastomas were concommitant findings.[7]

ARRHENOBLASTOMA

The arrhenoblastoma, although a rare ovarian tumor, is the most common of the masculinizing tumors. Attention was first directed to this tumor in 1905 by Pick.[8] Meyer, in 1930, studied a series of these tumors and originated the term "arrhenoblastoma." Pedowitz and O'Brien, in 1960, found 240 reported cases that they would accept as arrhenoblastomas and added two cases of their own. The incidence of malignancy in their series was 21.3 per cent.[7]

Less than 5 per cent of these tumors are bilateral.[9] They average 12-14 cm. in diameter and may range from a few millimeters to as large as a man's head or larger. The largest arrhenoblastoma reported measured 28 cm. in diameter and weighed 4,640 grams.[6]

Histologically, the arrhenoblastoma has been divided into three types by Meyer, based on the degree of differentiation of the tumor cells into tubules:

1. The tubular adenoma is the most differentiated type and it is composed of round tubular or gland-lik structures. This type is usually hormonally inactive.

2. The second type is the intermediate type which contains varying proportions of sarcomatous cells with

abortive attempts at tubule formation. This type is almost always associated with masculization.

3. The third type is the sarcomatous type. It is the least differentiated of the three forms. It exhibits a sarcomatous pattern resembling ovarian stroma in which are found clumps or columns of polyhedral cells. This type is always associated with masculization.

Our case is that of:

D. R., #1049: Admitted June 16, 1960

This was a gravida I, para I, female complaining of prolonged menstrual periods with intermenstrual spotting and a rapidly enlarging abdomino-pelvic mass of six-months' duration. Menarche—age 13, cycle—28 days, duration—3 days. Past history was essentially negative.

Physical Examination: Blood pressure 200/120. General—Well developed, well nourished Negro female in no distress. HEENT—Negative. Chest—Clear to percussion and auscultation. Breast—4 cm. firm, non-tender mass in the upper quadrant of the left breast. Heart—Normal sinus rhythm, Grade II systolic murmur heard over the entire precordium. Abdomen—Abdomino-pelvic mass enlarged to approximately five months' gestation. Bimanual examination confirmed the above findings.

The patient was taken to surgery on June 17, 1960 and had a bilateral salpingo-oophorectomy, total abdominal hysterectomy and a partial omentectomy. A 25x23x 10 cm. mass was removed and microscopically diagnosed as an arrhenoblastoma with possible malignant changes.

The patient returned to the hospital one month later and had a radical mastectomy for scirrhous carcinoma of the left breast.

The case in which the thecoma showed virilization is that of:

H. B., #145-076: Admitted September 8, 1956.

This was a 31-year-old nulligravida whose last normal menstrual period was May 14, 1956, admitted with a four months' history of amenorrhea. She had previously had a two months' period of amenorrhea one year prior to admission. Menarche—age 13, Cycle 30 days, duration —4 days with severe dysmenorrhea. She had been married for 14 years with a normal libido and no dyspareunia. There was a history of hirsutism of one year's duration and hoarseness for two months. She also complained of occasional stabbing pains in the lower abdomen.

Past History: Hypertension for one year. Diabetes—One year's duration. Appendectomy two years prior to this admission.

Physical Examination: Blood pressure 160/108, Pulse 68. General—well developed, well nourished Negro female in no distress. HEENT—moderate facial hirsutism. Tortuosity of the arterioles in the fundi. Chest—moderate hirsutism. Lungs—Clear to percussion and auscultation. Heart—normal sinus rhythm, no murmur. Abdomen—protuberant, male hair pattern. Supra-public midline scar. No masses palpated. Vaginal examination—clitoris enlarged; Introitus—marital. Vagina—normal. Corpus—normal size and position. Adnexa—firm, tender 4x4x3 cm. mass on the left. Extremities—whitish striae on the gluteal region and thighs.

17 Ketosteroids—17.34 mg.

Gonadotrophins—negative.

The patient was taken to surgery on September 21, 1956 and had a left ovarian cystectomy and a biopsy of the right ovary. The cyst measured 3x1.5x1 cm. and was diagnosed microscopically as a thecoma.

HILUS CELL TUMORS

The hilus of the human ovary contains nests of cells morphologically identical to testicular Leydig cells. These cells are almost always found in contiguity with the non-myelinated nerves of the hilus. Because of this almost constant anatomic relationship to the non-myelinated nerves, Berger, in 1923, used the term "sympathicotropic" to describe the hilus cell.[10] This cell has also been called "ovarian Leydig," interstitial cell and extraglandular Leydig cell.

The hilus cell is frequently a fairly characteristic one and is easily distinguishable from other lipoid or clear cells. It is usually smaller with a disproportionately large dark nucleus and generally has an acidophilic cytoplasm. The main source of confusion is distinguishing the hilus cell from regressing lutein cells, however, in most instances the lutein cell presents a more or less festooned appearance. The presence of Reinke crystalloids is diagnostic for both Leydig cells and the hilus cells, however, their absence in no way serves to invalidate the diagnosis of hilus cells, for in less than half of the reported cases of hilus cell tumors have these crystalloids been demonstrated.

The tumors are rarely large and only one reported is larger than 5 cm. All have been unilateral and, in no case has there been evidence of malignancy or recurrence. To date, 19 cases of hilus cell tumors have been reported. Clinically, these tumors are almost uniformly associated with hirsutism and amenorrhea, is a rule, in menstruating patients. Enlargement of the clitoris, acne, and voice changes have not been constant findings. Hilus cell tumors are found predominantly in older women. Only 4 of the 19 patients were less than 45 years of age. While virilism has been reported in all but two of the cases, paradoxically, the endometrium, which was available in approximately half of the cases, showed a hyperplastic pattern.[4] The case in our series which is representative of these tumors is that of:

C. S., #125-228: Admitted April 21, 1959.

This was a 30-year-old gravida 10, para 7, ab. 2, female who was admitted to the Obstetrical Service on

April 21, 1959, last normal menstrual period August 10, 1958. She was admitted with a diagnosis of hypertensive vascular disease with superimposed pre-eclampsia. She was known to have been hypertensive for five years.

On admission she complained of severe headaches, located in the frontal and supraorbital areas, associated with blurring of vision. A history of shortness of breath on exertion and palpitation was elicited. Weight gain during this pregnancy was 43 pounds. Menarche—age 11, cycle—28 days, and duration 3-5 days.

Physical Examination: Blood pressure 160/120, Pulse 76. General—well developed, moderately obese female in no acute distress. Eyes—decreased A/V ratio and moderate nicking of the vessels. Heart—normal sinus rhythm, Grade I systolic murmur at the left sternal border. Breasts—negative. Abdomen—uterus enlarged to 3 fingers below the zyphoid. Fetal heart tones—144. Tenderness present in the left lumbar region. Extremities—grade I pretibial edema. Vaginal examination—cervix soft, uneffaced and undilated. Vertex presentation at Station—3 (minus 3).

The patient failed to respond to antihypertensive medication and on April 26, 1959 a caesarean section was performed and a male infant was delivered. During surgery a 10x8x4 cm. left ovarian tumor was found and excised and diagnosed microscopically as a hilus cell neoplasm.

Although this case is not associated with virilization, it presents two interesting features: 1) association with pregnancy; and 2) following surgery, the patient became normotensive and has remained so. The only other case of hilus cell tumor associated with pregnancy was reviewed by Young in 1951 and this was in a 27-year-old who showed marked hirsutism during pregnancy which regressed after surgery.[11]

GYNANDROBLASTOMA

The term "gynandroblastoma" was first used by Meyer in 1930.[11] It was used to designate an ovarian tumor containing morphologically identifiable male and female cellular elements in the form of arrhenoblastoma and granulosa cell tumors. Clinically, his patient, similar to ours, demonstrated features characteristic of both androgen and estrogen production. Ten valid cases of gynandroblastoma have been reported.[13]

The preoperative diagnosis of gynandroblastoma is always uncertain because of the difficulty in predicting tumor type from the clinical syndrome. The paradoxical presence of masculinization with feminization, however, should make one suspect the diagnosis. Our case is that of:

M. G., #138-500: Admitted February 4, 1956.[14]

This was a 70-year-old gravida 2, para 2, female who was 30 years postmenopausal. She was admitted with a history of intermittent genital bleeding of three months' duration requiring the use of 9-10 pads on some days. In addition to the bleeding, she complained of lower left quadrant abdominal pain. Approximately five years prior to admission. She began to grow a beard and a mustache which required daily shaving. Two to three years later she had a remarkable return of libido. No voice changes were noted.

Physical examination showed an elderly Negro female who appeared younger than her stated age. There was hair on her chin and lip, but her body contour was that of a normal woman. Blood pressure was 140/80, Pulse 80.

Pelvic examination showed a clitoris which measured 3.5 cm. in length and 1.25 in diameter. There was a Bartholin cyst on the left approximately 3 cm. in diameter. The mucosa of the vagina appeared normal and the cervix was small, normal in color and showed no lesions. The uterus was slightly enlarged and firm. A huge cystic mass was palpated in the right adnexal region extending 4 cm. above the umbilicus. A small non-cystic mass was palpated in the left adnexa.

An endometrical curettage on February 10, 1956, at which time a uterus with fibroids, both tubes, a large cystic structure from the right adnexa and the left ovary were removed. The mass from the right adnexa measured 15x9x7 cm. and was microscopically diagnosed as a gynandroblastoma.

Sixteen months following surgery there was a striking diminution in hirsutism, the clitoris was one-half its preoperative size, and the patient reported a noticeable regression of the libido.

SUMMARY

During the ten year period from July 1952 through June 1962, 14 functioning ovarian tumors were found at Freedmen's Hospital. In this group of tumors there were seven granulosa cell tumors, three thecomas (one of which showed masculinizing symptoms), one luetoma, one arrhenoblastoma, one hilus cell tumor and one gynandroblastoma. Typical case histories from each of these groups are presented and the literature is reviewed.

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CURRENT DATA ON SUICIDES

In the United States the rate of suicide deaths for males is considerably higher than the rate for females. The death rate for whites is above that for non-whites. The western states have the highest rate and the southern states have the lowest. Suicides occur more frequently among the single, divorced and widowed than among the married. They occur at all economic levels with no preference for any one economic group. And they are more frequent among the older age groups.

Male suicides far exceed female suicides for both whites and non-whites. This is true for all age groups. Most authorities seem to agree that economic pressures and responsibilities for family maintenance rest more heavily on the male of the species.

The interesting thing about the differential between whites and non-whites is the contrast between rates in the middle Atlantic and South Atlantic areas of the United States. There would be more migrant Negroes in the Middle Atlantic states and more native Negroes in the South Atlantic states. The suicide curve for non-whites in the Middle Atlantic states more nearly parallels that of the whites than it does in the South Atlantic states. In fact, the rate for non-whites even exceeds that for whites in the 25-34 age groups.

Our national vital statistics in the East-North Central states and in the East-South Central states show essentially the same divergence in suicide curves for whites and non-whites in the north and south. The data indicated that the difference in suicide rates between whites and non-whites is not because of any racial characteristics but more likely as the result of economic and social pressures. Migrants in general have higher suicide rates than natives which probably reflects social and economic pressures.

Suicides increase sharply in times of economic depression. There was a jump (literally) following the 1929 stock market crash. The rate reached an all time peak at the depth of the depression in the early 1930's. Then it gradually declined until the war years of the 1940's when it was in a deep trough. The rate increased sharply after the war and then gradually decreased again until it reached a new low at the time of the Korean crisis. Now that unemployment is climbing, and will probably stay relatively high even in prosperous times, we are experiencing another rise, particularly in the 15-24 year age group where first jobs after school are hard to get.

Suicide is mainly a cause of death of the older age groups. Many of those moving to California for retirement find the same competition with natives that other migrants do. They find that life isn't so easy as they expected and they miss their friends back East. Some may find that their children have no place or time for them out there and they take the suicide way out of their troubles.

Los Angeles has one of the best known suicide prevention centers in the country. Its staff of investigators tries to trace every suspected suicide in the area. In addition to physical autopsies they hold psychological autopsies. These consist of conferences of experts who discuss the psychological factors in the victim's life which might have precipitated his suicidal act. They interview members of his family and his friends and bring together all available records which might throw light on his emotional problems. As a consequence they have found that many cases originally classified as deaths from natural or accidental causes are really suicides. Other prevention centers are in Boston, New York, Miami and Chicago.

In 1952, Metropolitan Life Insurance Company disbursed $5,442,000 in claims for deaths due to suicide. In 1962, this figure had doubled to $10,365,000. This is the fourth largest amount paid out for a specific cause of death.

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